

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :

A61L 27/00, A61F 2/06

A1

(11) International Publication Number:

WO 97/10011

(43) International Publication Date:

20 March 1997 (20.03.97)

(21) International Application Number: PCT/US96/14195

(22) International Filing Date: 5 September 1996 (05.09.96)

(30) Priority Data:

08/526,273

11 September 1995 (11.09.95)

US

663,490

13 June 1996 (13.06.96)

US

(71) Applicant: SCHNEIDER (USA) INC. [US/US]; 5905 Nathan Lane, Plymouth, MN 55442 (US).

(72) Inventors: DING, Ni; 4365 Juneau Lane, Plymouth, MN 55446 (US). HELMUS, Michael, N.; 4400 Lime Avenue, Long Beach, CA 90807 (US).

(74) Agents: ROTHERY, Brian, M. et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).

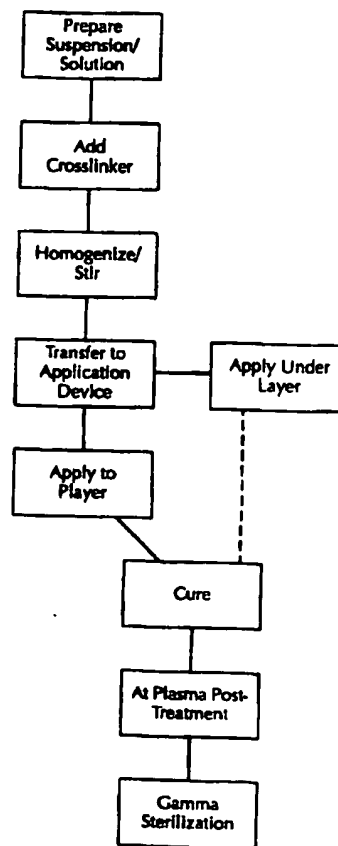
(81) Designated States: AU, BR, CA, IL, JP, KR, MX, NO, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published*With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.***BEST AVAILABLE COPY**

(54) Title: DRUG RELEASE STENT COATING PROCESS

(57) Abstract

A method of coating implantable open lattice metallic stent prosthesis is disclosed which includes sequentially applying a plurality of relatively thin outer layers of a coating composition comprising a solvent mixture of uncured polymeric silicone material and crosslinker and finely divided biologically active species, possibly of controlled average particle size, to form a coating on each stent surface. The coatings are cured in situ and the coated, cured prostheses are sterilized in a step that includes preferred pretreatment with argon gas plasma and exposure to gamma radiation electron beam, ethylene oxide, steam.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

DRUG RELEASE STENT COATING PROCESS

BACKGROUND OF THE INVENTION

I. Cross-Reference to Related Applications

5 The present application is a Continuation-In-Part of co-pending application Serial No. 08/526,273, filed September 11, 1995, and a Continuation-In-Part of co-pending application Serial No. 08/424,884, filed April 19, 1995, all portions of the parent applications
10 not contained in this application being deemed incorporated by reference for any purpose. Cross-reference is also made to application Serial No. 08/663,518 entitled "DRUG RELEASE STENT COATING AND
15 PROCESS", filed of even date and of common inventorship and assignee, that is also a Continuation-In-Part of both above-referenced patent applications. Any portion of that application that is not contained herein is also deemed to be incorporated by reference for any purpose.

II. Field of the Invention

20 The present invention relates generally to therapeutic expandable stent prosthesis for implantation in body lumens, e.g., vascular implantation and, more particularly, to a process for providing biostable elastomeric coatings on such stents which incorporate
25 biologically active species having controlled release characteristics directly in the coating structure.

II. Related Art

 In surgical or other related invasive medicinal procedures, the insertion and expansion of stent devices
30 in blood vessels, urinary tracts or other difficult to

-2-

access places for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions has become a common form of long-term treatment. Typically, such prosthesis are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released to expand or be expanded in situ. These devices are generally designed as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

One type of self-expanding stent has a flexible tubular body formed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. The elements are wound in a common direction, but are displaced axially relative to each other and meet, under crossing a like number of elements also so axially displaced, but having the opposite direction of winding. This configuration provides a resilient braided tubular structure which assumes stable dimensions upon relaxation. Axial tension produces elongation and corresponding diameter contraction that allows the stent to be mounted on a catheter device and conveyed through the vascular system as a narrow elongated device. Once tension is relaxed in situ, the device at least substantially reverts to its original shape. Prosthesis of the class including a braided flexible tubular body are illustrated and described in

U.S. Patents 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al.

Implanted stents have also been used to carry medicinal agents, such as thrombolytic agents. U.S. Patent 5,163,952 to Froix discloses a thermal memoried expanding plastic stent device which can be formulated to carry a medicinal agent by utilizing the material of the stent itself as an inert polymeric drug carrier. Pinchuk, in U.S. Patent 5,092,877, discloses a stent of a polymeric material which may be employed with a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Patent 4,916,193, and MacGregor, U.S. Patent 4,994,071. Sahatjian in U.S. Patent No. 5,304,121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug; possible drugs include cell growth inhibitors and heparin. A further method of making a coated intravascular stent carrying a therapeutic material in which a polymer coating is dissolved in a solvent and the therapeutic material dispersed in the solvent and the solvent thereafter evaporated is described in Berg et al, U.S. Patent 5,464,650, issued November 5, 1995 and corresponding to European patent application 0 623 354 A1 published 09 November 1994.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design-- A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material

and Process Engineering Technical Conference (1990) relates to polymer/drug/membrane systems for releasing heparin. Those polymer/drug/membrane systems require two distinct layers to function.

5 The above cross-referenced grandparent application supplies an approach that provides long-term drug release, i.e., over a period of days or even months, incorporated in a controlled-release system. The parent application and present invention provide a process for
10 coating such stents including techniques that enable the initial burst effect of drug elation to be controlled and the drug release kinetic profile associated with long-term therapeutic effect to be modified.

 Metal stents of like thickness and weave generally
15 have better mechanical properties than polymeric stents.

 Metallic vascular stents braided of even relatively fine metal filament can provide a large amount of strength to resist inwardly directed circumferential pressure in blood vessels. In order for a polymer
20 material to provide comparable strength characteristics, a much thicker-walled structure or heavier, denser filament weave is required. This, in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space
25 available in the structure. In addition, when applicable, it is usually more difficult to load and deliver polymeric stents using vascular catheter delivery systems.

 It will be noted, however, that while certain types
30 of stents such as braided metal stents may be superior

to others for some applications, the process of the present invention is not limited in that respect and may be used to coat a wide variety of devices. The present invention also applies, for example, to the class of
5 stents that are not self-expanding including those which can be expanded, for instance, with a balloon. Polymeric stents of all kinds can be coated using the process. Thus, regardless of particular detailed
10 embodiments the use of the invention is not considered or intended to be limited with respect either to stent design or materials of construction. Further, the present invention may be utilized with other types of implant prostheses.

Accordingly, it is a primary object of the present
15 invention to provide a coating process for coating a stent to be used as a deployed stent prosthesis, the coating being capable of long-term delivery of biologically active materials.

Another object of the invention is to provide a
20 process for coating a stent prosthesis using a biostable hydrophobic elastomer in which biologically active species are incorporated within a cured coating.

Still another object of the present invention is to provide a multi-layer coating in which the percentage of
25 active material can vary from layer to layer.

A further object of the present invention is to control or modify aspects of the timed or time variable drug delivery from a stent coating by controlling average particle size in the biologically active
30 species.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

5

SUMMARY OF THE INVENTION

The present invention provides processes for producing a relatively thin layer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the
10 surfaces of a deployable stent prosthesis. The preferred stent to be coated is a self-expanding, open-ended tubular stent prosthesis. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of
15 an open braid of fine single or polyfilament metal wire which flexes without collapsing and readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter. The stent resiliently attempts to resume predetermined stable dimensions upon
20 relaxation in situ.

The coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of
25 such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finely divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate
30 mixtures. The active material is dispersed in a carrier

-7-

material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state. In some applications the coating may further be characterized as a composite initial tie coat or undercoat and a composite topcoat. The coating thickness ratio of the topcoat to the undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations.

The coating may be applied by dipping or spraying using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. Thereafter the polymeric precursor material is cured at room temperature or elevated temperatures or the solvent evaporated away from the dissolved polymer as the case may be. Curing is defined as the process of converting

the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which include physical-chemical changes. Where, for example, polyurethane thermoplastic elastomers are used, solvent evaporation can occur at room temperature rendering the polymeric material useful for controlled drug release without further curing. Non-limiting examples of curing according to this definition include the application of heat and/or chemical agents and the evaporation of solvent which may induce physical and/or chemical changes.

The ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. These materials are applied as pre-polymer in the coating composition and must thereafter be cured. The preferred species have a relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90°C for a period of time such as 16 hours. A curing step may be implemented both after application of a certain number of lower undercoat layers and the topcoat layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a postcure sterilization process which includes an inert gas plasma treatment, and then exposure to gamma

radiation, electron beam, ethylene oxide (ETO) or steam sterilization may also be employed.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is
5 purged with nitrogen and a vacuum applied to about 20-50mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a
10 power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to about 100-450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon
15 atmosphere for an additional period of time, typically five minutes.

After the argon plasma pretreatment, the coated and cured stents are subjected to gamma radiation sterilization nominally at 2.5-3.5 Mrad. The stents
20 enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status. It has been found that constrained stents subjected to gamma sterilization without utilizing the argon plasma pretreatment lose resiliency and do not recover at a
25 sufficient or appropriate rate.

The elastomeric material that forms a major constituent of the stent coating should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade
30 and which minimizes tissue rejection and tissue

inflammation and one which will undergo encapsulation by tissue adjacent to the stent implantation site.

Polymers suitable for such coatings include silicones (e.g., polysiloxanes and substituted polysiloxanes),
5 polyurethanes (including polycarbonate urethanes), thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and polyamide elastomers. The above-referenced materials are considered hydrophobic with respect to the
10 contemplated environment of the invention.

Agents suitable for incorporation include antithrobotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, antiinflammatories, agents that inhibit hyperplasia and in particular
15 restenosis, smooth muscle cell inhibitors, antibiotics, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive
20 action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

25 The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemorial alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and
30 Phynox®. Further details concerning the fabrication and

-11-

details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Patents 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al. To the extent additional information
5 contained in the above-referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of
10 interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism
15 depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the
20 encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths
25 connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which a material released traverses through another material.

The desired release rate profile can be tailored by
30 varying the coating thickness, the radial distribution

-12-

(layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a crosslink structure of greater density will increase release time and reduce burst effect.

Additionally, with eluting materials such as heparin, release kinetics, particularly initial drug release rate, can be affected by varying the average dispersed particle size. The observed initial release rate or burst effect may be substantially reduced by using smaller particles, particularly if the particle size is controlled to be less than about 15 microns and the effect is even more significant in the particle size range of less than or equal to 10 microns, especially when the coating thickness is not more than about 50 μ m and drug loading is about 25-45 weight percent.

It will also be appreciated that an unmedicated silicone thin top layer provides an advantage over drug containing top coat. Its surface has a limited porosity and is generally smooth, which may be less thrombogeneous and may reduce the chance to develop

-13-

calcification, which occurs most often on the porous surface.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate
5 like parts throughout the same:

FIGURE 1 is a schematic flow diagram illustrating the steps of the process of the invention;

FIGURE 2 represents a release profile for a multi-layer system showing the percentage of heparin released
10 over a two-week period;

FIGURE 3 represents a release profile for a multi-layer system showing the relative release rate of heparin over a two-week period;

FIGURE 4 illustrates a profile of release kinetics
15 for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period;

FIGURE 5 illustrates drug elution kinetics at a given loading of heparin over a two-week period at
20 different coating thicknesses;

FIGURE 6 illustrates the release kinetics in a coating having a given tie-layer thickness for different top coat thicknesses in which the percentage heparin in the tie coat and top coats are kept constant;

25 FIGURE 7 illustrates the release kinetics of several coatings having an average coating thickness of 25 microns and a heparin loading of 37.5% but using four different average particle sizes;

FIGURES 8-11 are photomicrographs of coated stent
30 fragments for the coatings of FIGURE 7 having a

-14-

corresponding average particle size of 4 microns, 17 microns, 22 microns and 30 microns, respectively.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in Figure 1. The coating solutions or suspensions are prepared at 10 as will be described later. The desired amount of crosslinking agent is added to the suspension/solution as at 12 and material is then agitated or stirred to produce a homogenous coating composition at 14 which is thereafter transferred to an application container or device which may be a container for spray painting at 16. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Coating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2-6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example:

-15-

W(silicone) = 5 g; solid percent = 35%; W(hep) = $5 \times 0.35 \times .375 / (0.625) = 1.05$ g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W(\text{silicone solid}) / V(\text{THF}) = 0.04$ for a 37.5% heparin coating solution. Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The crosslinker may be any suitable and compatible agent including platinum and peroxide based materials. The solution was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Coating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: W(silicone) = 5 g; for a 10% dexamethasone coating, $W(\text{dex}) = 5 \times 0.35 \times 0.1 / 0.9 = 0.194$ g and THF needed in the coating solution calculated. $W(\text{silicone solid}) / V(\text{THF}) = 0.06$ for a 10% dexamethasone coating solution. Example: W(silicone) = 5 g; $V(\text{THF}) = 5 \times 0.35 / 0.06 = 29.17$ ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added.

-16-

The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was
5 transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the
10 stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, typically a paint jar attached to an air brush, such as
15 a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0-160 psi). Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately
20 1-1.7 atm. (15-25) psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the
25 relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the
30 desired coating speed, nominally about 40 rpm.

-17-

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2-4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, for a coating level of 3-4 mg of heparin per cm^2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30-50 rpm and with a spray nozzle flow rate in the range of 4-10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the tie layer as at 18 and thereafter additional upper

layers, which may be of a different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, are applied as the top layer as at 20. The application of the top layer follows the same coating procedure as the tie layer with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by modifying the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at 22 in Figure 1, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50°C) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90°C or higher for approximately 16 hours. The temperature may be raised to as high as 150°C for dexamethasone containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers, and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at 24 is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, CA). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 MHz and from 0-500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 42.55 cm (16.75 inches) by 34.3 cm (13.5 inches) by 44.45 cm (17.5 inches) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20-50mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma

treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to 100-450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at 26, the stents are exposed to gamma sterilization at 2.5-3.5 Mrad. The radiation may be carried out with the stent in either the radially non-constrained status - or in the radially constrained status.

With respect to the anticoagulant material heparin, the percentage in the tie layer is nominally from about 20-50% and that of the top layer from about 0-30% active material. The coating thickness ratio of the top layer to the tie layer varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subcute thrombosis.

Figure 4 depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in Figure 5. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the top layer as shown by the same drug loading and similar tie-coat thickness in Figure 6.

The effect of average particle size is depicted in the FIGURES 7-11 in which coating layers with an average coating thickness of about 25 microns (μm), prepared and sterilized as above, were provided with dispersed heparin particles (to 37.5% heparin) of several different average particle sizes. FIGURE 7 shows plots of elution kinetics for four different sizes of embedded heparin particles. The release took place in phosphate buffer (pH 7.4) at 37°C. The release rate using smaller, particularly 4-6 μm average sized particles noticeably reduces the initial rate or burst effect and thereafter the elution rate decreases more slowly with time. Average particle sizes above about 15 μm result in initial release rates approaching bolus elution. This, of course, is less desirable, both from the standpoint of being an unnecessary initial excess and for prematurely depleting the coating of deserved drug material.

In addition, as shown in the photomicrographs of FIGURES 8-11, as the average particle size increases, the morphology of the coating surface also changes.

Coatings containing larger particles (FIGURES 9-11) have very rough and irregular surface characteristics. These surface irregularities may be more thrombogenic or exhibit an increased tendency to cause embolization when the corresponding stent is implanted in a blood vessel.

Accordingly, it has been found that the average particle size should generally be controlled below about 15 μm to reduce the burst effect and preferably should be less than or equal to about 10 μm for best results. The 4-6 μm size worked quite successfully in the laboratory. However, it should be noted that larger particle size can also be advantageously used, for instance, when the drug load is low, such as below 25 weight percent. Elution kinetics can be adjusted by a combination of changing the particle size and changing the load or concentration of the dispersed drug material.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be modified to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and anti-thrombotic drugs in the topcoat layer. In this manner, the anti-thrombotic drugs, for example, heparin, will elute first followed by antiproliferation drugs,

-23-

e.g. dexamethasone, to better enable safe encapsulation of the implanted stent.

The heparin concentration measurements were made utilizing a standard curve prepared by complexing
5 azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at
10 approximately 37°C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the
15 elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In
20 the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a
25 thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need
30 for utilizing biodegradable or reabsorbable vehicles for

carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

5 Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the
10 technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having
15 two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a
20 desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin
25 release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which
30 result in a great deal of flexibility with respect to

controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed
5 layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

10 Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active
15 species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in
20 considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the
25 invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

-26-

CLAIMS

We claim:

1. A method of coating an implantable prosthesis with a layer comprising an hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom comprising the steps of:
 - (a) applying a formulation containing polymeric material in solvent mixture and an amount of finely divided biologically active species;
 - (b) curing said polymeric material; and
 - (c) wherein the average particle size of the finely divided biological species in said coating formulation is selected to affect delivery kinetics.
2. The method of claim 1 wherein the elastomeric material is selected from the group consisting of silicones, polyurethanes, polyamide elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.
3. The method of claim 1 wherein the biologically active material has an average particle size less than or equal to about 15 μm .
4. The method of claim 2 wherein the biologically active material includes heparin.
5. The method of claim 4 wherein the layer comprises about 25-45 weight percent biologically active material.

6. The method of claim 1 wherein the biologically active material has an average particle size less than or equal to 10 μm .

7. The method of claim 6 wherein the biologically active material includes heparin.

8. A method of controlling the kinetics of an eluting (biologically active) particulate material incorporated in a polymeric coating in an implantable prosthesis comprising the step of controlling the average particle size below a designated maximum size.

9. The method of claim 7 wherein said biologically active material is heparin and the average particle size is less than or equal to about 15 μm .

10. The method of claim 9 wherein the layer comprises about 25-45 weight percent biologically active material.

11. A method of controlling the kinetics of an eluting (biologically active) particulate material incorporated in a polymer coating in an implantable prosthesis comprising the steps of selecting an average particle size and a drug load to produce desired delivery kinetics.

12. The method of claim 11 further comprising the steps of selecting an average particle size and a drug load to produce a substantially smooth surface on the prosthesis.

13. The method of claim 11 wherein the layer comprises about 25-45 weight percent biologically active material.

-28-

14. The method of claim 13 wherein said biologically active material is heparin and the average particle size is less than or equal to about 15 μm .

15. A coated implantable prosthesis having an external surface covered with a conformal coating comprising a hydrophobic elastomeric material incorporating an amount of biologically active material in particulate form dispersed therein for timed delivery therefrom wherein the delivery kinetics thereof is controlled at least in part by variations in parameters selected from the group consisting of average particle size and concentration of dispersed material in said coating or a combination thereof.

16. The device of claim 15 wherein the delivery kinetics are controlled by variations in particle size.

17. The device of claim 15 wherein the elastomeric material is selected from the group consisting of silicones, polyurethanes, polyamide elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.

18. The device of claim 15 wherein the biologically active material has an average particle size less than or equal to about 15 μm .

19. The device of claim 18 wherein the biologically active material includes heparin.

20. The device of claim 15 wherein the layer comprises about 25-45 weight percent biologically active material.

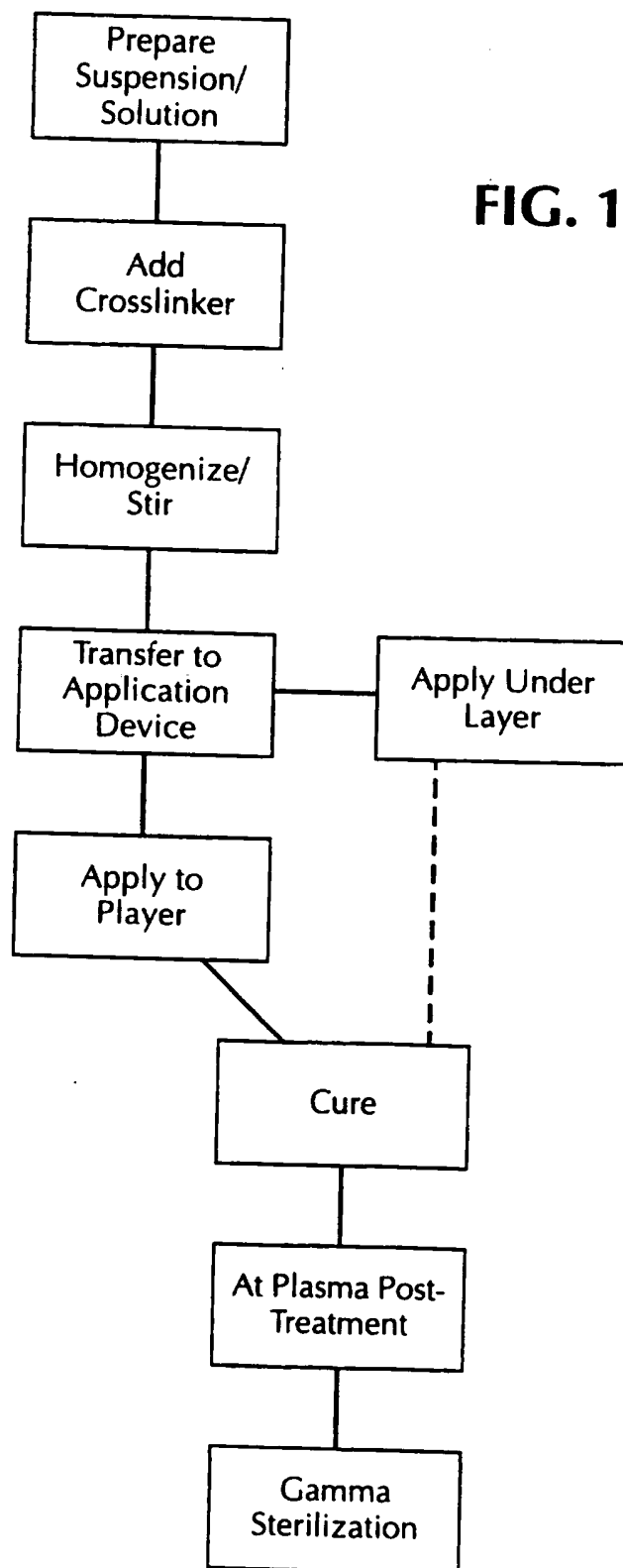
21. The device of claim 15 wherein the biologically active material has an average particle size less than or equal to 10 μm .

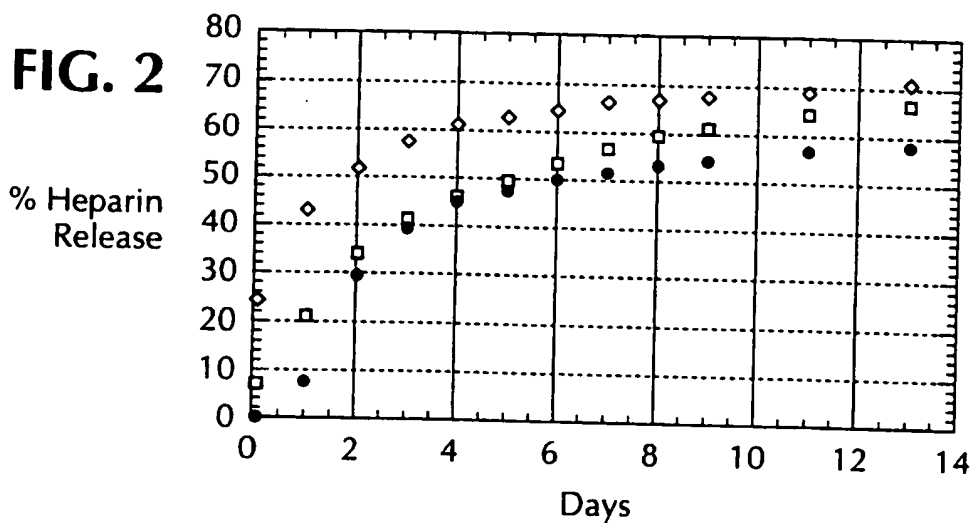
22. The device of claim 21 wherein the
5 biologically active material includes heparin.

23. The device of claim 15 wherein the layer comprises about 25-45 weight percent biologically active material and wherein the biologically active material is heparin having an average particle size less than or
10 equal to 10 microns.

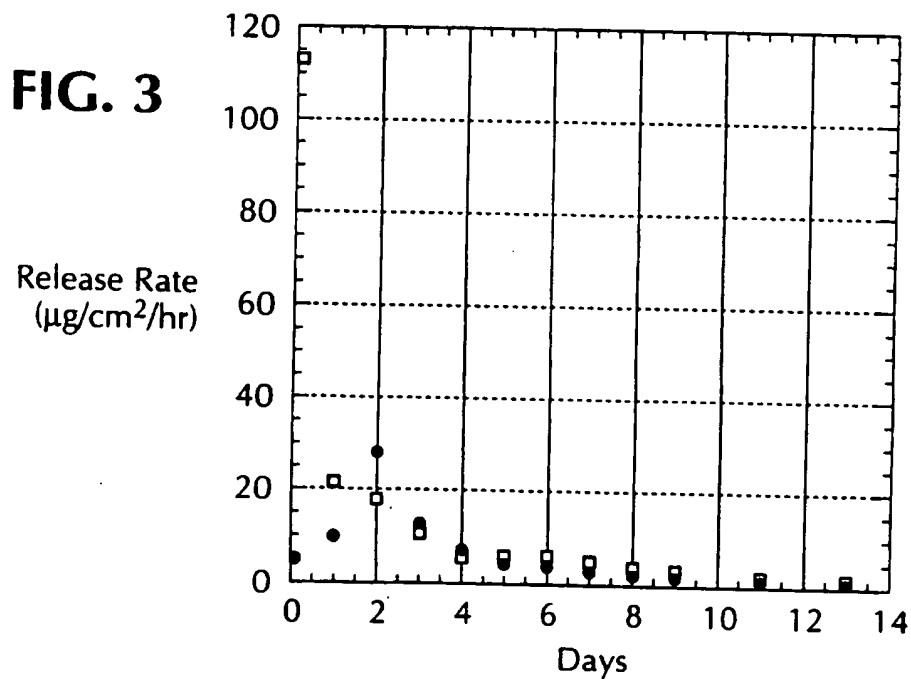
24. A coated implantable prosthesis having an external surface covered with a coating comprising an elastomeric material incorporating an amount of biologically active material having an average particle
15 size less than or equal to about 15 μm dispersed in the elastomeric material.

FIG. 1





- Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
- Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating
- ◇ Single Layer 37.5% Hep. Coating



- Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
- Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating

FIG. 4

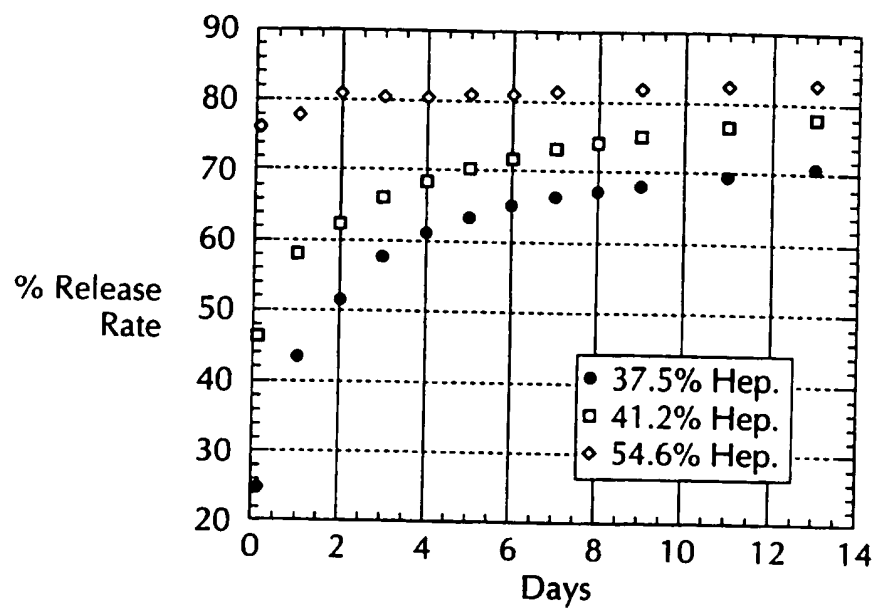


FIG. 5

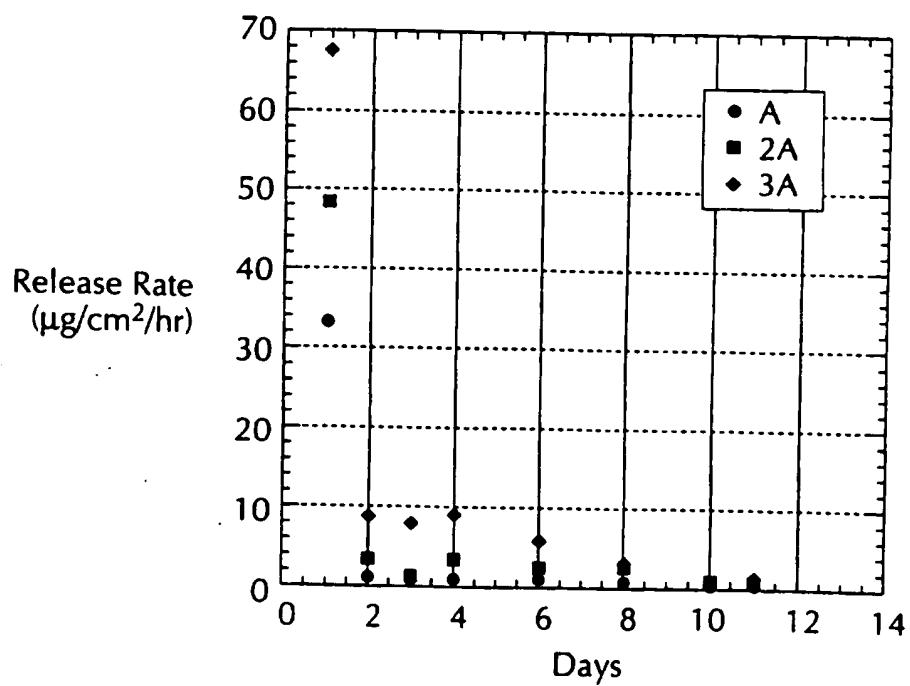
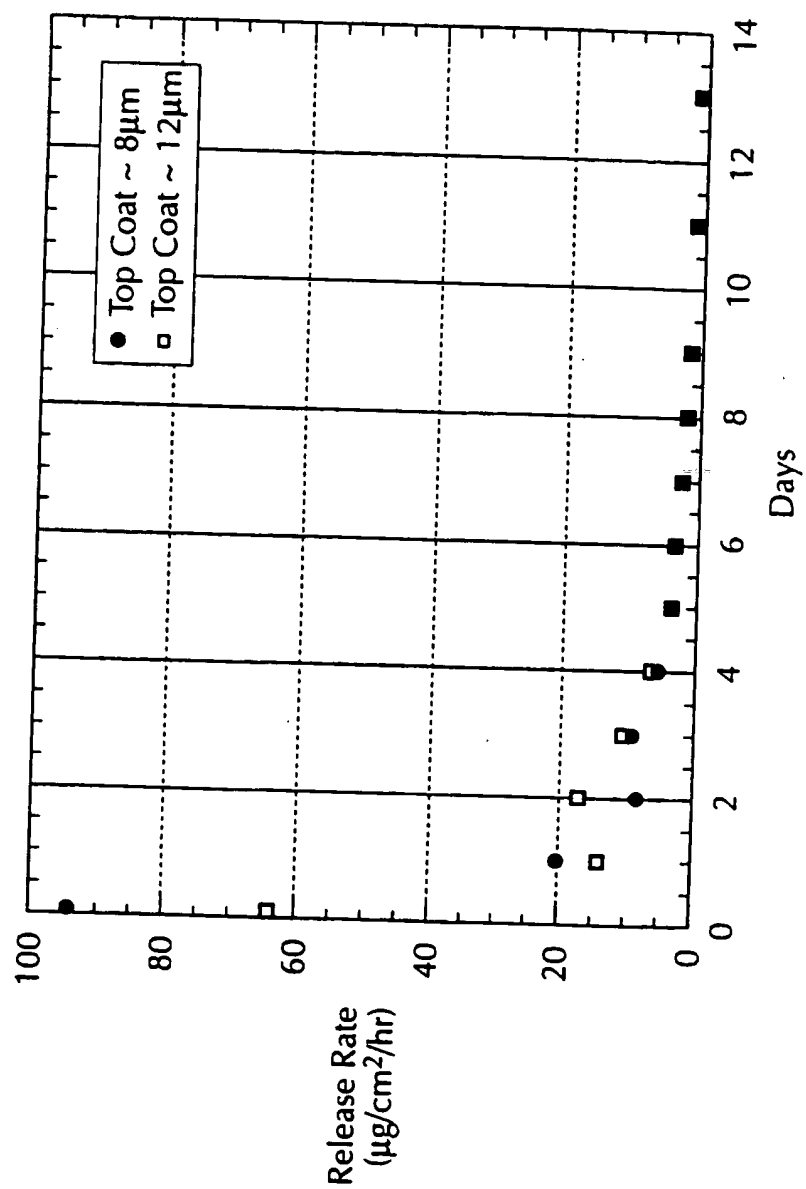


FIG. 6



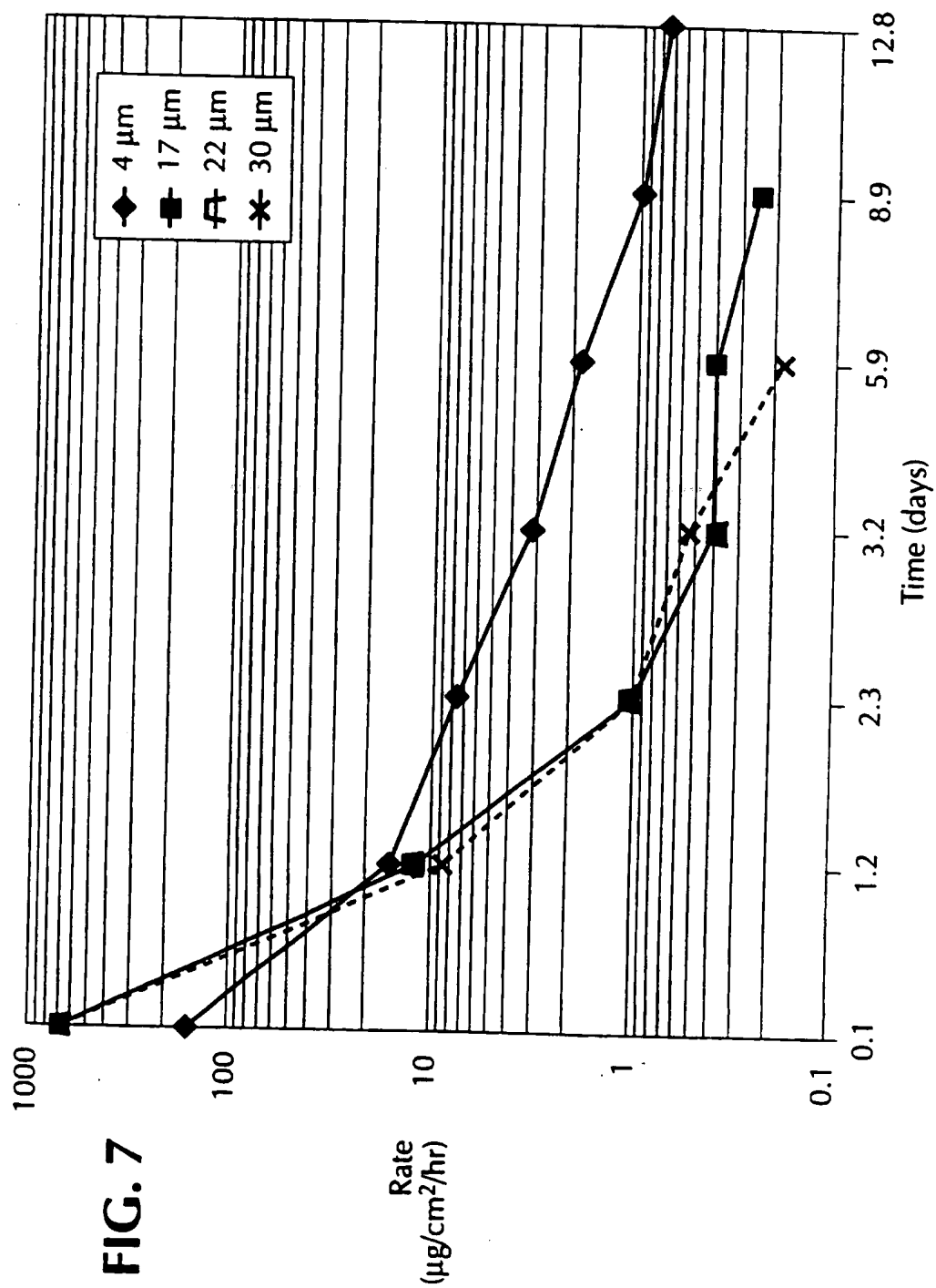


FIG. 8

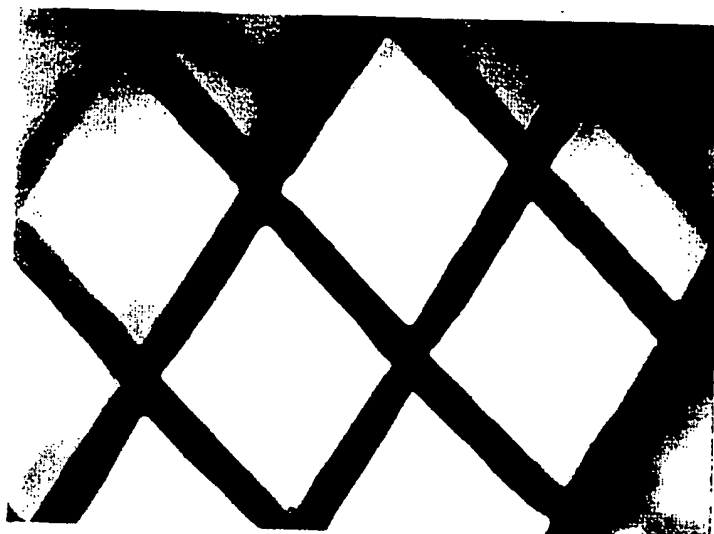


FIG. 9



FIG. 10



FIG. 11



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/14195

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61L27/00 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 623 354 (MEDTRONIC) 9 November 1994 cited in the application see page 3, line 13 - line 14 see page 4, line 20 - line 30; claims 1,6,7,14	1,2,4,5, 15,17,20
A	--- WO,A,92 15286 (NOVA PHARMACEUTICAL) 17 September 1992 see claims 1,8-10	1-24
A	--- WO,A,94 21309 (D.S.B.) 29 September 1994 see the whole document	1
A	--- WO,A,94 21308 (CEDARS-SINAI MEDICAL CENTER) 29 September 1994 see page 5, line 17; claims 1,8,19 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

13 January 1997

Date of mailing of the international search report

28 01. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Peltre, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-623354	09-11-94	US-A- 5464650	07-11-95
		JP-A- 8033718	06-02-96
WO-A-9215286	17-09-92	AU-A- 1579092	06-10-92
		US-A- 5437656	01-08-95
		US-A- 5344411	06-09-94
		US-A- 5512055	30-04-96
WO-A-9421309	29-09-94	BE-A- 1006819	13-12-94
		AU-A- 6178094	11-10-94
WO-A-9421308	29-09-94	EP-A- 0689465	03-01-96
		JP-T- 8507715	20-08-96
		US-A- 5562922	08-10-96

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☐ FADED TEXT OR DRAWING

☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.